Remarks

Upon entry of the foregoing amendment, claims 1, 5-7, 9, 13, 14, 16, 18, 21, 25-28, 30, 32-38, 40-42, 44-47, 50, 51, 53, 54, 57, 60, 63-72 and 75-83 are pending in the application, with claims 1, 27, 41, 63 and 75 being the independent claims. Claim 39 has been canceled and rewritten as claim 83. Claims 52 and 59 have been canceled without prejudice to or disclaimer of the subject matter therein. Claims 1, 6, 27, 37, 38, 46, 75 and 81 have been amended. Claim 1 has been amended such that it is now directed to a limited number of well specified diseases. Support for this amendment can be found, *inter alia*, at page 40, line 21, through page 43, line 21, and in claims 36, 38 and 40 of the application as filed. Solely for internal consistency, in claim 1, the term "an animal" has been amended to "a mammal." Claims 6 and 46 have been amended to emphasize that these claims and the claims dependent thereon all relate to compounds which are indolopyrans, and therefore within Group I of the restriction requirement within the previous Office Action (Paper No. 7, page 2, lines 7-15). Claim 27 has been amended to independent form. Claims 37 and 38 have been amended to conform the dependencies with the amendments to claim 1. In claims 75 and 81, the term "indolopyran" has been amended to "compound" according to the Examiner's suggestion. In claim 81, the term "napthyl" has been amended to "naphthyl" to correct an obvious typographical error.

New claims 82 and 83 have been added. Support for new claim 82 can be found, *inter alia*, at page 43, lines 7-21, and in claim 38 of the application as filed. Support for

new claim 83 can be found, *inter alia*, at page 42, lines 10-25, and in claim 39 of the application as filed.

These amendments are believed to introduce no new subject matter and their entry is respectfully requested.

I. Allowable Subject Matter

Applicants note with appreciation the Examiner's statement that "[c]laims 41, 42, 44, 45, 63-72, 78, [and] 80 appear to be allowable." Office Action, page 6, line 13.

II. Election/Restriction

A. Paper No. 7

The Office Action that was mailed on June 5, 2001 (Paper No. 7), contained a restriction requirement (*see* page 2, lines 7-15). In the Amendment and Reply filed on November 5, 2001, Applicants traversed this restriction requirement as follows:

> The Examiner has required the election/restriction of the claims under 35 U.S.C. § 121, to one of the following two groups of claims:
>
> I. Claims 1-7, 9, 11-14, 16, 18, 21, 23, 25-28, 30, 32-47, 49-51, 53-54, 57-58, 60, 63-72, drawn to the formula I in claim 1 where Y is CN, A is phenyl or carbocyclic aryl, B is indolo, X is O, Z is NR_8R_9, and R_8 and R_9 are hydrogen; and

> II. Claims 1-78, drawn to the formula I in claim 1 where the radicals are all moieties not defined in group I, classified in various classes and subclasses.
>
> (*See* Office Action, page 2, lines 8-15).
>
> Applicants elect the invention of group I for prosecution in the present application. This election is made with traverse. Applicants reserve the right to file one or more applications directed to the subject matter of the non-elected claims.
>
> The Examiner has defined group I to be compounds where Z is NR_8R_9 wherein R_8 and R_9 are hydrogen. (Office Action, page 2, lines 11-12). Applicants traverse to the extent that expansion of the definition of group I to include compounds where Z is NR_8R_9 wherein R_8 and R_9 are *independently H or* C_{1-4}*alkyl* would not alter the classification of the claimed compounds and would not place an undue burden on the Examiner.

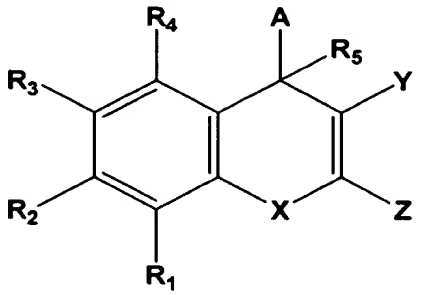
Amendment and Reply, November 5, 2001, page 16, line 4, through page 17, line 3. Applicants have not yet received a reply to this traversal. Therefore, Applicants respectfully request that the Examiner reply to this traversal.

B. Paper No. 12

In the present Office Action, the Examiner has revised the restriction requirement at Paper No. 7 "to restrict out claims 6, 7, 9, 13, 14, 18, 21, 25 and 46-47, 50, 51, 52-54, 57, and 59-60 and include them in group II since they concern compounds of formula II." Office Action, page 2, lines 5-7. Applicants respectfully traverse this revised restriction requirement.

Claims 52 and 59 have been canceled. Claim 6 is directed to:

6. (Twice amended) The method of claim 1, wherein said compound has the Formula II:



(II)

or a pharmaceutically acceptable salt or prodrug thereof, wherein:

(a) R_1-R_4 are independently hydrogen, halo, haloalkyl, aryl, [fused aryl,] carbocyclic, a heterocyclic group, a heteroaryl group, C_{1-10} alkyl, alkenyl, alkynyl, arylalkyl, arylalkenyl, arylalkynyl, heteroarylalkyl, heteroarylalkenyl, heteroarylalkynyl, carbocycloalkyl, heterocycloalkyl, hydroxyalkyl, aminoalkyl, carboxyalkyl, nitro, amino, cyano, acylamido, hydroxy, thiol, acyloxy, azido, alkoxy, carboxy, methylenedioxy, carbonylamido or alkylthiol; [and] provided that R_1 and R_2, or R_2 and R_3, or R_3 and R_4, taken together with the atoms to which they are attached form a pyrrolo group, wherein said group is optionally substituted;

(b) the aryl portion of said arylalkyl, the aryl portion of said arylalkenyl and the aryl portion of said arylalkynyl are each independently C_{6-14} aryl;

(c) said carbocyclic is C_{3-8} cycloalkyl or C_{3-8} cycloalkenyl;

(d) said heteroaryl, the heteroaryl portion of said heteroarylalkyl, the heteroaryl portion of said heteroarylkenyl and the heteroaryl portion of said heteroarylalkynyl are each independently selected from the group consisting of thienyl, benzo[b]thienyl, naphtho[2,3-b]thienyl, thianthrenyl, furyl, pyranyl, isobenzofuranyl, chromenyl, xanthenyl, phenoxanthiinyl, 2*H*-pyrrolyl, pyrrolyl, imidazolyl, pyrazolyl, pyridyl, pyrazinyl, pyrimidinyl, pyridazinyl, indolizinyl, isoindolyl, 3*H*-indolyl, indolyl, indazolyl, purinyl, 4*H*-quinolizinyl, isoquinolyl, quinolyl, phthalzinyl, naphthyridinyl, quinozalinyl, cinnolinyl, pteridinyl, carbazolyl, β-carbolinyl, phenanthridinyl, acrindinyl, perimidinyl, phenanthrolinyl, phenazinyl, isothiazolyl, phenothiazinyl, isoxazolyl, furazanyl, phenoxazinyl, 1,4-dihydroquinoxaline-2,3-dione, 7-aminoisocoumarin, pyrido[1,2-a]pyrimidin-4-one, 1,2-benzoisoxazol-3-yl, benzimidazolyl, 2-oxindolyl 2-oxobenzimidazolyl and the N-oxides thereof; and

(e) said heterocyclic and the heterocyclic portion of said heterocycloalkyl are each independently selected from the group

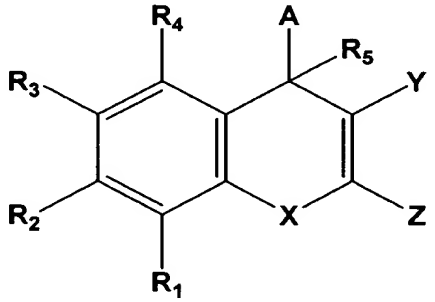
consisting of tetrahydrofuranyl, pyranyl, piperidinyl, piperazinyl, pyrrolidinyl, imidazolidinyl, imidazolinyl, indolinyl, isoindolinyl, quinuclidinyl, morpholinyl, isochromanyl, chromanyl, pyrazolidinyl pyrazolinyl, tetronoyl and tetramoyl.

Claims 7, 9, 13, 14, 18, 21 and 25 are directly or indirectly dependent on claim 6.

For compounds of claim 6, R_1 and R_2, or R_2 and R_3, or R_3 and R_4, taken together with the atoms to which they are attached form a pyrrolo group, wherein said group is optionally substituted. Thus, all of claims 6, 7, 9, 13, 14, 18, 21 and 25 are indolopyrans falling within the definition of compounds of claim 1 (i.e., Formula I as well as Formula II). Therefore, all of claims 6, 7, 9, 13, 14, 18, 21 and 25 are compounds of Group I and *not* compounds of Group II.

Claim 46 is directed to:

46. (Twice amended) The pharmaceutical composition of claim 41, comprising a pharmaceutically acceptable excipient or carrier and a compound of Formula II:



(II)

or a pharmaceutically acceptable salt or prodrug thereof, wherein:

(a) R_1-R_4 are independently hydrogen, halo, haloalkyl, aryl, [fused aryl,] carbocyclic, a heterocyclic group, a heteroaryl group, C_{1-10} alkyl, alkenyl, alkynyl, arylalkyl, arylalkenyl, arylalkynyl, heteroarylalkyl, heteroarylalkenyl, heteroarylalkynyl, carbocycloalkyl, heterocycloalkyl, hydroxyalkyl, aminoalkyl, carboxyalkyl, nitro, amino, cyano, acylamido, hydroxy, thiol, acyloxy, azido, alkoxy, carboxy, methylenedioxy, carbonylamido or alkylthiol; [and] <u>provided that</u> R_1 and R_2, or R_2 and R_3, or R_3 and R_4, taken together with the atoms to which

they are attached form a pyrrolo group, wherein said group is optionally substituted;

(b) the aryl portion of said arylalkyl, the aryl portion of said arylalkenyl and the aryl portion of said arylalkynyl are each independently C_{6-14} aryl;

(c) said carbocyclic is C_{3-8} cycloalkyl or C_{3-8} cycloalkenyl;

(d) said heteroaryl, the heteroaryl portion of said heteroarylalkyl, the heteroaryl portion of said heteroarylkenyl and the heteroaryl portion of said heteroarylalkynyl are each independently selected from the group consisting of thienyl, benzo[b]thienyl, naphtho[2,3-b]thienyl, thianthrenyl, furyl, pyranyl, isobenzofuranyl, chromenyl, xanthenyl, phenoxanthiinyl, 2*H*-pyrrolyl, pyrrolyl, imidazolyl, pyrazolyl, pyridyl, pyrazinyl, pyrimidinyl, pyridazinyl, indolizinyl, isoindolyl, 3*H*-indolyl, indolyl, indazolyl, purinyl, 4*H*-quinolizinyl, isoquinolyl, quinolyl, phthalzinyl, naphthyridinyl, quinozalinyl, cinnolinyl, pteridinyl, carbazolyl, β-carbolinyl, phenanthridinyl, acrindinyl, perimidinyl, phenanthrolinyl, phenazinyl, isothiazolyl, phenothiazinyl, isoxazolyl, furazanyl, phenoxazinyl, 1,4-dihydroquinoxaline-2,3-dione, 7-aminoisocoumarin, pyrido[1,2-a]pyrimidin-4-one, 1,2-benzoisoxazol-3-yl, benzimidazolyl, 2-oxindolyl 2-oxobenzimidazolyl and the N-oxides thereof; and

(e) said heterocyclic and the heterocyclic portion of said heterocycloalkyl are each independently selected from the group consisting of tetrahydrofuranyl, pyranyl, piperidinyl, piperazinyl, pyrrolidinyl, imidazolidinyl, imidazolinyl, indolinyl, isoindolinyl, quinuclidinyl, morpholinyl, isochromanyl, chromanyl, pyrazolidinyl pyrazolinyl, tetronoyl and tetramoyl.

Claims 47, 50, 51, 53, 54, 57 and 60 are directly or indirectly dependent upon claim 46.

For compounds of claim 46, R_1 and R_2, or R_2 and R_3, or R_3 and R_4, taken together with the atoms to which they are attached form a pyrrolo group. Thus, all of claims 46, 47, 50, 51, 53, 54, 57 and 60 are indolopyrans falling within the definition of compounds of claim 41 (i.e., Formula I as well as Formula II). Therefore, all of claims 46, 47, 50, 51, 53, 54, 57 and 60 are compounds of Group I and *not* compounds of Group II.

For the reasons stated above, Applicants respectfully submit that this revised restriction requirement should be withdrawn.

Furthermore, Applicants have responded to an election of species requirement (*see* Paper No. 2, sections 1 and 3) by electing the species 2-amino-3-cyano-4-(3-bromo-4,5-dimethoxyphenyl)-4H-indolo[4,5-b]pyran for initial examination (*see* Reply To Requirement For Election Of Species, filed April 16, 2001). Claims 52 and 59 have been canceled. All of claims 6, 7, 9, 13, 14, 18, 21, 25 and 46-47, 50, 51, 53, 54, 57, and 60 read on the elected species. Therefore, Applicants respectfully submit that the revised restriction requirement is improper and should be withdrawn.

III. Rejections Under § 112, First Paragraph

A. Claim 28

1. Primary Argument

The examiner has rejected claim 28 under 35 U.S.C. § 112, first paragraph. (Office Action, page 2, line 15). Applicants respectfully traverse this rejection.

Specifically, the Examiner is of the opinion that:

> [T]he specification, does not reasonably provide enablement for the method of treating all of the various cancers. No drug can treat all of these cancers. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims. The claims as recited are broader than the scope of enablement.

(Office Action, page 2, lines 16-21). Applicants respectfully disagree with the Examiner's analysis and conclusions.

The specification provides explicit enablement for the formulation of pharmaceutical preparations (*see, e.g.,* page 45, line 16, through page 47, line 31). The specification further provides explicit enablement for dosages and methods of administration (*see, e.g.*, page 43, line 23, through page 44, line 24). The specification also describes a method for treating cancer wherein the cancer is selected from the group consisting of:

> Hodgkin's disease, non-Hodgkin's lymphoma, acute and chronic lymphocytic leukemias, multiple myeloma, neuroblastoma, breast carcinomas, ovarian carcinomas, lung carcinomas, Wilms' tumor, cervical carcinomas, testicular carcinomas, soft-tissue sarcomas, chronic lymphocytic leukemia, primary macroglobulinemia, bladder carcinomas, chronic granulocytic leukemia, primary brain carcinomas, malignant melanoma, small-cell lung carcinomas, stomach carcinomas, colon carcinomas, malignant pancreatic insulinoma, malignant carcinoid carcinomas, malignant melanomas, choriocarcinomas, mycosis fungoides, head and neck carcinomas, osteogenic sarcoma, pancreatic carcinomas, acute granulocytic leukemia, hairy cell leukemia, neuroblastoma, rhabdomyosarcoma, Kaposi's sarcoma, genitourinary carcinoma, thyroid carcinomas, esophageal carcinomas, malignant hypercalcemia, cervical hyperplasia, renal cell carcinomas, endometrial carcinomas, polycythemia vera, essential thrombocytosis, adrenal cortex carcinomas, skin cancer, and prostatic carcinomas.

See, e.g., the paragraph bridging pages 37 and 38 of the application as filed.

The Examiner is of the opinion that "the specification, does not reasonably provide enablement for the method of treating *all* of the various cancers [mentioned]." (Office Action, page 2, lines 16-17) (emphasis added). The implication is that the Examiner is of the opinion that the specification enables the treatment of some of the

cancers listed in claim 28 but not others. However, the Examiner has provided no evidence in support of her opinion. The Examiner's further statements ("The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims. The claims as recited are broader than the scope of enablement.") (Office Action, page 2, lines 18-21) merely state the conclusion. These statements do not provide any evidence as to why one of ordinary skill in the art would be of the opinion that the full scope of claim 28 is not enabled. "[I]t is incumbent upon the Patent Office, whenever a rejection on this basis is made, to explain *why* it doubts the truth or accuracy of any statement in a supporting disclosure and to back up assertions of its own with acceptable evidence or reasoning which is inconsistent with the contested statement." *In re Marzocchi*, 439 F.2d 220, 224, 169 USPQ 367, 370 (CCPA 1971). *See also* M.P.E.P., Rev. 1, Feb. 2000, § 2164.04 ("Burden on the Examiner Under the Enablement Requirement").

Furthermore, cancer cells are, *inter alia*, characterized not only by a loss of cell cycle control but also by resistance to apoptosis. *See generally* Raymond W. Ruddon, *Biochemistry of Cancer, in* Holand-Frei Cancer Medicine, Chapter 2 (Robert C. Blast, Jr., *et al.* eds., 5th ed., B.C. Decker, 2000), an electronic copy of which is attached herewith in a Second Supplemental Information Disclosure Statement as Document AT15. Consequently, increasing the rate of apoptosis is recognized by those of ordinary skill in the art as an effective method for the treatment of a wide variety of cancers. *See, e.g.*, WO 00/04901, page 3, line 3, through page 5, line 6, a copy of which was previously

submitted in a Supplemental Information Disclosure Statement as Document AO2. Indeed, caspase activation is recognized, by those of ordinary skill in the art of cancer therapy, as a crucial requirement for the sensitivity of tumor cells toward drug-induced cell death. *See, e.g.,* Maret Los, *et al.*, "Cross-Resistance fo CD95- and Drug-Induced Apoptosis as a Consequence of Deficient Activation of Caspases (ICE/Ced-3 Proteases)," *Blood 90*:3118-3129, 3128 (1997), a copy of which has previously been submitted as Document AS10.

For the reasons stated above, Applicants respectfully submit that the Examiner has not met the burden of establishing a *prima facie* case for non-enablement of claim 28, under 35 U.S.C. § 112, first paragraph, and the rejection should be withdrawn.

2. Secondary Arguments

In support of this rejection, the Examiner has, *inter alia*, made the following comments:

> In terms of the fifth Wands factor [the level of predictability in the art], the caspase potency ranges from 7 which is poor to 364 which [is] great. There are massive differences in caspase potency for small changes in structure. For example, compound 97 has a 3 bromo instead of a 2 bromo and a methyl on the 4H-indolo ring. However, the caspase potency [of] compound [97 is] 7 whereas it is 364 for compound 95. The level of predictability regarding caspase potency is low.

Office Action, page 3, lines 16-22. Applicants respectfully disagree.

As a preliminary matter, the caspase potencies cited by the Examiner were measured as EC_{50} values for compounds applied to ZR-75-1 cells. EC_{50} is the calculated

concentration resulting in 50% of the maximum fluorescent emission under the conditions of the caspase activity assay described as Example 148, at page 93, line 4, through page 94, last line, of the application as filed. Thus, a relatively low number (*e.g.*, 7) indicates that a compound is a relatively potent activator of caspase activity; while a relatively high number (*e.g.*, 364) indicates that a compound is a relatively less potent activator of caspase activity.

The variation noted by the Examiner does not lead to the conclusion reached by the Examiner for at least two reasons. First, there is no requirement under U.S. patent statutes or regulations that all embodiments of an invention have the same or similar efficacy. Indeed, "[i]t is not a function of the claims to specifically exclude . . . possible inoperative substances . . . ." *In re Dinh-Nguyen*, 492 F.2d 856, 858-59, 181 USPQ 46, 48 CCPA 1974) (emphasis omitted). *Accord*, *Atlas Powder Co. v. E.I. Du Pont De Nemours*, 750 F.2d 1569, 1576 (1984). Therefore, the Examiner's opinion that "[t]here are massive differences in caspase potency for small changes in structure" (Office Action, page 3, lines 17-19) is not probative to the patentability of claim 28.

Second, assuming, *arguendo*, that the compounds noted by the Examiner do have different potencies for inducing apoptosis in ZR-75-1 cells, this does not provide one of ordinary skill in the art with any reason to believe that compounds noted by the Examiner would not induce apoptosis in the cancers listed in claim 28 of the present invention. Therefore, the Examiner's opinion that "[t]he level of predictability regarding caspase potency is low" (Office Action, page 3, lines 21-22), is not probative to the patentability of claim 28.

In support of this rejection, the Examiner has also stated that "[I]n terms of the sixth Wands factor, the amount of direction provided by the inventor is poor, because the applicant does not test compounds for their affects on the specific diseases claimed. *The applicant must show results for the cancers claimed involving specific cell lines.*" Office Action, page 3, line 22, through page 4, line 2 (emphasis added). Applicants respectfully disagree.

There is no requirement in U.S. patent statutes or regulations that the applicant "show test results for the cancers claimed involving specific cell lines." To the contrary, "it is incumbent upon the Patent Office, whenever a rejection [under 35 U.S.C. § 112, first paragraph] is made, to explain *why* it doubts the truth or accuracy of any statement in a supporting disclosure and to back up assertions of its own with acceptable evidence or reasoning which is inconsistent with the contested statement." *In re Marzocchi*, 439 F.2d 220, 224, 169 USPQ 367, 370 (CCPA 1971).

Applicants respectfully submit that the Examiner has provided no factual support for the rejection of claim 28, under 35 U.S.C. § 112, first paragraph. Therefore, the Examiner has not established a *prima facie* case; and the rejection should be withdrawn.

B. Claims 1, 5, 26 and 79

The Examiner has rejected claims 1, 5, 26 and 79 under 35 U.S.C. § 112, first paragraph. Office Action, page 4, line 15. Applicants respectfully traverse this rejection.

Specifically, the Examiner is of the opinion that:

> [T]he specification[] does not reasonably provide enablement for the method of treating all diseases related to a disorder responsive to the induction of apoptosis in an animal suffering therefrom. The induction of apoptosis in a mammal is a mechanism not a disease. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims. The claims as recited are broader than the scope of enablement.

Office Action, page 4, lines 16-22. Applicants respectfully disagree.

Claim 1 is an independent claim. Claims 5, 26 and 79 are dependent upon claim 1. In the interest of advancing the prosecution of this application, claim1 has been amended such that it is now directed to:

> 1. (Once amended) A method of treating a disorder responsive to the induction of apoptosis in a mammal suffering therefrom, wherein said disorder is selected from the group consisting of:
> (a) an autoimmune disease;
> (b) inflammation; and
> (c) a skin disease;
> comprising . . . .

Therefore, claim 1 is directed to the treatment of a limited of number of well defined diseases. The specification does enable one of ordinary skill in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with this claim. Applicants respectfully submit that the rejection of claims 1, 5, 26 and 79 under 35 U.S.C. § 112, first paragraph, has been accommodated and should be withdrawn.

IV. Rejections Under 35 U.S.C. § 112, Second Paragraph

The Examiner has rejected claims 75 and 81 under 35 U.S.C. § 112, second paragraph, as being indefinite. Office Action, page 6, lines 6-8. Applicants respectfully traverse this rejection.

Specifically, the Examiner is of the opinion that: "the term 'indolopyran' is indefinite because it is not a statutory class of invention. The [term] 'compound' is suggested." Office Action, page 6, lines 9-10. Applicants respectfully disagree.

35 U.S.C. § 101 provides that:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Neither 35 U.S.C. § 101 nor 35 U.S.C. § 112, require that a statutory class of invention appear as the first noun in the preamble of a claim. An "indolopyran" is a "compound," and a "compound" is a "composition of matter." Therefore, the words "indolopyran" and "compound" are equally valid as initial nouns in the preamble of a claim.

However, solely in the interests of advancing the prosecution of this application, claims 75 and 81 have been amended according to the Examiner's suggestion. Applicants respectfully submit that the rejection of claims 75 and 81 under 35 U.S.C. § 112, second paragraph, has been accommodated and should be withdrawn.

V. Objection

The Examiner has objected to claims 27, 30, 32-35, 36-40, 76 and 77 "because they are based on a rejected claim." Office Action, page 6, lines 11-12. Applicants respectfully traverse this objection.

Claim 27 has been amended to be independent. Claims 30-35 are directly or indirectly dependent upon claim 27. As described in section IV, above, independent claim 75 has been amended according to the Examiner's suggestion. Claims 76 and 77 are directly or indirectly dependent upon claim 75.

Thus, claims 27, 30, 32-35, 76 and 77 are not based upon a rejected claim. In view of the amendments and remarks above, Applicants respectfully submit that claims 27, 30, 32-35, 36-40, 76 and 77 are now fully in condition for allowance.

Prompt and favorable consideration of this Amendment and Reply is respectfully requested.

Respectfully submitted,

STERNE, KESSLER, GOLDSTEIN & FOX P.L.L.C.

Bruce E. Chalker

Bruce E. Chalker
Attorney for Applicants
Registration No. 47,480

Date: April 25, 2002

1100 New York Avenue, N.W.
Suite 600
Washington, D.C. 20005-3934
(202) 371-2600

Version with markings to show changes made

In the claims:

Claims 39, 52 and 59 have been canceled without prejudice or disclaimer.

Claims 1, 6, 27, 37, 38, 46, 75 and 81 have been amended as follows:

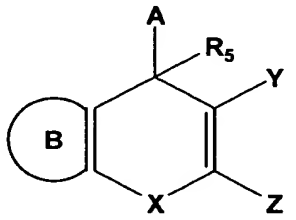
1. (Twice amended) A method of treating a disorder responsive to the induction of apoptosis in [an animal] a mammal suffering therefrom, wherein said disorder is selected from the group consisting of:

(a) an autoimmune disease;

(b) inflammation; and

(c) a skin disease;

comprising administering to [a] said mammal [in need of such treatment] an effective amount of a compound of Formula I:



(I)

or a pharmaceutically acceptable salt or prodrug thereof, wherein:

X is O;

Y is CN;

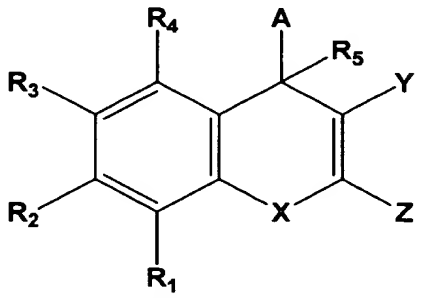
Z is NR_8R_9, wherein R_8 and R_9 are independently H or C_{1-4}alkyl;

R_5 is hydrogen or C_{1-10} alkyl;

A is optionally substituted C_{6-14} aryl; and

B is an optionally substituted indolo ring.

6. (Twice amended) The method of claim 1, wherein said compound has the Formula II:



(II)

or a pharmaceutically acceptable salt or prodrug thereof, wherein:

(a) R_1-R_4 are independently hydrogen, halo, haloalkyl, aryl, [fused aryl,] carbocyclic, a heterocyclic group, a heteroaryl group, C_{1-10} alkyl, alkenyl, alkynyl, arylalkyl, arylalkenyl, arylalkynyl, heteroarylalkyl, heteroarylalkenyl, heteroarylalkynyl, carbocycloalkyl, heterocycloalkyl, hydroxyalkyl, aminoalkyl, carboxyalkyl, nitro, amino, cyano, acylamido, hydroxy, thiol, acyloxy, azido, alkoxy, carboxy, methylenedioxy, carbonylamido or alkylthiol; [and] <u>provided that</u> R_1 and R_2, or R_2 and R_3, or R_3 and R_4, taken together with the atoms to which they are attached form a pyrrolo group, wherein said group is optionally substituted;

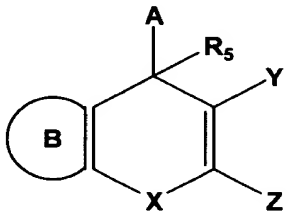
(b) the aryl portion of said arylalkyl, the aryl portion of said arylalkenyl and the aryl portion of said arylalkynyl are each independently C_{6-14} aryl;

(c) said carbocyclic is C_{3-8} cycloalkyl or C_{3-8} cycloalkenyl;

(d) said heteroaryl, the heteroaryl portion of said heteroarylalkyl, the heteroaryl portion of said heteroarylkenyl and the heteroaryl portion of said heteroarylalkynyl are each independently selected from the group consisting of thienyl, benzo[b]thienyl, naphtho[2,3-b]thienyl, thianthrenyl, furyl, pyranyl, isobenzofuranyl, chromenyl, xanthenyl, phenoxanthiinyl, 2*H*-pyrrolyl, pyrrolyl, imidazolyl, pyrazolyl, pyridyl, pyrazinyl, pyrimidinyl, pyridazinyl, indolizinyl, isoindolyl, 3*H*-indolyl, indolyl, indazolyl, purinyl, 4*H*-quinolizinyl, isoquinolyl, quinolyl, phthalzinyl, naphthyridinyl, quinozalinyl, cinnolinyl, pteridinyl, carbazolyl, β-carbolinyl, phenanthridinyl, acrindinyl, perimidinyl, phenanthrolinyl, phenazinyl, isothiazolyl, phenothiazinyl, isoxazolyl, furazanyl, phenoxazinyl, 1,4-dihydroquinoxaline-2,3-dione, 7-aminoisocoumarin, pyrido[1,2-a]pyrimidin-4-one, 1,2-benzoisoxazol-3-yl, benzimidazolyl, 2-oxindolyl 2-oxobenzimidazolyl and the N-oxides thereof; and

(e) said heterocyclic and the heterocyclic portion of said heterocycloalkyl are each independently selected from the group consisting of tetrahydrofuranyl, pyranyl, piperidinyl, piperazinyl, pyrrolidinyl, imidazolidinyl, imidazolinyl, indolinyl, isoindolinyl, quinuclidinyl, morpholinyl, isochromanyl, chromanyl, pyrazolidinyl pyrazolinyl, tetronoyl and tetramoyl.

27. (Once amended) [The method of claim 1] A method of treating a disorder responsive to the induction of apoptosis in a mammal suffering therefrom, wherein said disorder is cancer, comprising administering to said mammal an effective amount of a compound of Formula I:



(I)

or a pharmaceutically acceptable salt or prodrug thereof, wherein:

X is O;

Y is CN;

Z is NR_8R_9, wherein R_8 and R_9 are independently H or C_{1-4}alkyl;

R_5 is hydrogen or C_{1-10} alkyl;

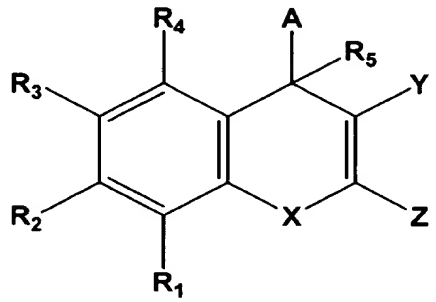
A is optionally substituted C_{6-14} aryl; and

B is an optionally substituted indolo ring.

37. The method of claim [1] 36, wherein said [disorder] autoimmune disease is rheumatoid arthritis.

38. The method of claim 1, wherein said disorder is inflammation[or inflammatory bowel disease].

46. (Twice amended) The pharmaceutical composition of claim 41, comprising a pharmaceutically acceptable excipient or carrier and a compound of Formula II:



(II)

or a pharmaceutically acceptable salt or prodrug thereof, wherein:

(a) R_1-R_4 are independently hydrogen, halo, haloalkyl, aryl, [fused aryl,] carbocyclic, a heterocyclic group, a heteroaryl group, C_{1-10} alkyl, alkenyl, alkynyl, arylalkyl, arylalkenyl, arylalkynyl, heteroarylalkyl, heteroarylalkenyl, heteroarylalkynyl, carbocycloalkyl, heterocycloalkyl, hydroxyalkyl, aminoalkyl, carboxyalkyl, nitro, amino, cyano, acylamido, hydroxy, thiol, acyloxy, azido, alkoxy, carboxy, methylenedioxy, carbonylamido or alkylthiol; [and] provided that R_1 and R_2, or R_2 and R_3, or R_3 and R_4, taken together with the atoms to which they are attached form a pyrrolo group, wherein said group is optionally substituted;

(b) the aryl portion of said arylalkyl, the aryl portion of said arylalkenyl and the aryl portion of said arylalkynyl are each independently C_{6-14} aryl;

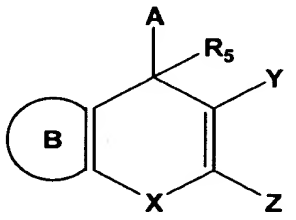
(c) said carbocyclic is C_{3-8} cycloalkyl or C_{3-8} cycloalkenyl;

(d) said heteroaryl, the heteroaryl portion of said heteroarylalkyl, the heteroaryl portion of said heteroarylkenyl and the heteroaryl portion of said

heteroarylalkynyl are each independently selected from the group consisting of thienyl, benzo[b]thienyl, naphtho[2,3-b]thienyl, thianthrenyl, furyl, pyranyl, isobenzofuranyl, chromenyl, xanthenyl, phenoxanthiinyl, 2*H*-pyrrolyl, pyrrolyl, imidazolyl, pyrazolyl, pyridyl, pyrazinyl, pyrimidinyl, pyridazinyl, indolizinyl, isoindolyl, 3*H*-indolyl, indolyl, indazolyl, purinyl, 4*H*-quinolizinyl, isoquinolyl, quinolyl, phthalzinyl, naphthyridinyl, quinozalinyl, cinnolinyl, pteridinyl, carbazolyl, β-carbolinyl, phenanthridinyl, acrindinyl, perimidinyl, phenanthrolinyl, phenazinyl, isothiazolyl, phenothiazinyl, isoxazolyl, furazanyl, phenoxazinyl, 1,4-dihydroquinoxaline-2,3-dione, 7-aminoisocoumarin, pyrido[1,2-a]pyrimidin-4-one, 1,2-benzoisoxazol-3-yl, benzimidazolyl, 2-oxindolyl 2-oxobenzimidazolyl and the N-oxides thereof; and

(e) said heterocyclic and the heterocyclic portion of said heterocycloalkyl are each independently selected from the group consisting of tetrahydrofuranyl, pyranyl, piperidinyl, piperazinyl, pyrrolidinyl, imidazolidinyl, imidazolinyl, indolinyl, isoindolinyl, quinuclidinyl, morpholinyl, isochromanyl, chromanyl, pyrazolidinyl pyrazolinyl, tetronoyl and tetramoyl.

75. (Twice amended) [An indolopyran] <u>A compound</u> of Formula I:



(I)

or a pharmaceutically acceptable salt or prodrug thereof, wherein:

B is optionally substituted indolo;

X is O;

Y is CN;

Z is NR_8R_9, wherein R_8 and R_9 are independently H or C_{1-4}alkyl;

R_5 is hydrogen or C_{1-10} alkyl; and

A is optionally substituted C_{6-14} aryl.

81. (Once amended) The [indolopyran] compound of claim 75, wherein said aryl is selected from the group consisting of phenyl, [napthyl] naphthyl, penanthrenyl, anthracenyl, indenyl, azulenyl, biphenyl, biphenylenyl and fluorenyl.

Claims 82 and 83 have been added.